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10/538,716	06/10/2005	Toshiya Fujisato	AKA-0286	6913
,	7590 11/20/2007 ITE, ZELANO & BRANI	GAN P.C	EXAM	INER
2200 CLARENDON BLVD.			MAKAR, KIMBERLY A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

		Application No.	Applicant(s)			
Office Action Summary		10/538,716	FUJISATO ET AL.			
		Examiner	Art Unit			
		Kimberly A. Makar, Ph.D.	1636			
Period fo	The MAILING DATE of this communication app or Reply	pears on the cover sheet with the c	correspondence address			
WHIC - Exte after - If NC - Failu Any earn	ORTENED STATUTORY PERIOD FOR REPLY CHEVER IS LONGER, FROM THE MAILING DANSIONS of time may be available under the provisions of 37 CFR 1.13 SIX (6) MONTHS from the mailing date of this communication. Operiod for reply is specified above, the maximum statutory period verse to reply within the set or extended period for reply will, by statute reply received by the Office later than three months after the mailing ed patent term adjustment. See 37 CFR 1.704(b).	ATE OF THIS COMMUNICATION 36(a). In no event, however, may a reply be tir will apply and will expire SIX (6) MONTHS from , cause the application to become ABANDONE	N. nely filed the mailing date of this communication. ED (35 U.S.C. § 133).			
Status						
1)⊠	Responsive to communication(s) filed on <u>04 September 2007</u> .					
• —	This action is FINAL . 2b) This action is non-final.					
3)	Since this application is in condition for allowance except for formal matters, prosecution as to the merits is					
•	closed in accordance with the practice under E	x parte Quayle, 1935 C.D. 11, 4	53 O.G. 213.			
Disposit	ion of Claims					
4)⊠	Claim(s) <u>4,5 and 7-11</u> is/are pending in the application.					
	4a) Of the above claim(s) is/are withdraw	wn from consideration.				
5)	Claim(s) is/are allowed.					
	Claim(s) 4,5 and 7-11 is/are rejected.					
•	Claim(s) is/are objected to.					
8)	Claim(s) are subject to restriction and/o	r election requirement.				
Applicat	ion Papers					
9)	The specification is objected to by the Examine	er.				
10)	The drawing(s) filed on is/are: a) acc	epted or b) objected to by the	Examiner.			
	Applicant may not request that any objection to the	drawing(s) be held in abeyance. Se	e 37 CFR 1.85(a).			
	Replacement drawing sheet(s) including the correct	- · · · · · · · · · · · · · · · · · · ·				
11)	The oath or declaration is objected to by the Ex	caminer. Note the attached Office	e Action or form PTO-152.			
Priority (under 35 U.S.C. § 119		. `			
	Acknowledgment is made of a claim for foreign All b) Some * c) None of:		ı)-(d) or (f).			
	1. Certified copies of the priority document		ion No			
	2. Certified copies of the priority document3. Copies of the certified copies of the priority					
	application from the International Bureau	<u>-</u>	ed iii tiiis National Stage			
* (See the attached detailed Office action for a list	, , , ,	ed.			
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Attachmer	nt(s) ce of References Cited (PTO-892)	4) 🔲 Interview Summary	, (PTO 413)			
	ce of References Cited (P10-692) ce of Draftsperson's Patent Drawing Review (PT0-948)	Paper No(s)/Mail D	Pate			
3) 🔲 Infor	mation Disclosure Statement(s) (PTO/SB/08) er No(s)/Mail Date	5) Notice of Informal F 6) Other:	Patent Application			

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DETAILED ACTION

Response to Amendments

- 1. Applicant's amendments to claims in the response filed 9/04/07 are acknowledged. Currently, claims 4-5, 7-11 are pending and under examination. In the previous office action, claims 2, 5, 7-8 and 10-11 were rejection under 103(a0 as being obvious over Giberson in view of Anderson et al. Claims 2, and 4-11 were rejected under 112 2nd paragraph for being indefinite. Any rejection not maintained in this office action is withdrawn.
- 2. The following rejection is necessitated by applicant's amendments. Applicant's amendments have narrowed the scope such that the treating solution contains a detergent. While this limitation was part of a generic Markush group of cancelled claim 2, previous art read on other species of the Markush group, and therefore was properly rejected.

For the purposes of prosecution the following is defined:

- 3. There is no teaching for a definition of decellularization. It is being defined as "the loss of at least a cell" from a tissue being treated according to the broadest reasonable interpretation of the claim limitation.
- 4. Claim 10 recites, "a method of decellularizing native tissue of mammalian origin comprising immersing said tissue in a treating solution, and irradiation the immersed tissue with microwaves while maintaining the temperature of the tissue in the range between 0°C and 40°C, whereby said tissue is decellularized." Using the broadest

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reasonable interpretation, this claim can be interpreted two ways: 1) immersing the tissue in a treating solution, and *then* irradiating the tissue with microwaves or 2) immersing the tissue in a treating solution, and while still immersed (or concurrently), irradiating the immersed tissue with microwaves. For the purposes of prosecution, the method is being read as, immersing the tissue in a treating solution, and while still immersed (or concurrently), irradiating the immersed tissue with microwaves.

Claim Rejections - 35 USC § 103

- 5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:
 - (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
- 6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).
- 7. Claims 5, 7-8 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giberson et al (US Patent Publication US20020177183) and

Anderson et al (US 5,571,216) in view of Essenfeld, (US Patent 6,207,408). Claims 5, 7-8, and 10-11 recite a method of decellularizing native tissue of mammalian origin comprising irradiating with microwaves immersed in a treating solution containing a detergent, while maintaining the temperature of the tissue in the range between 0°C and 40°C, whereby said tissue is decellularized (claim 10). The method is further limited wherein where said tissue is soft tissue (claim 5) or an organ or part thereof (claim 7). The method is further limited comprising a step of washing said tissue with a fresh washing liquid following irradiation (claim 8). The method is further limited wherein said tissue is immersed in said treating solution received in a microwave-transmitting container which is in turn in heat exchange contact with a coolant liquid received in a microwave-transmitting vessel, and wherein said tissue is irradiated with microwaves in a microwave oven while circulating said coolant liquid through an external cooling apparatus (claim 11).

8. The preamble of the claims, "a method of decellularizing native tissue" bears no patentable weight, as this appears to be the result of the microwaving immersed tissue in any treating solution while maintaining the temperature within a wide range. A preamble is generally not given any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness, but instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 197 F.2d 150, 152, 88 USPQ 578, 481 (CCPA 1951). Absent evidence to the contrary, any method which performs the same

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steps of microwaving immersed tissue in any treating solution while maintaining the temperature within the same range teaches the same method.

- 9. As noted above, the phrase "decellularized" is not defined in the specification. There is no teaching of how much a tissue is decellularized to read on the phrase, nor at point the tissue qualifies as decellularized. Using the broadest reasonable interpretation, the loss of a single cell during the process renders the treated tissue decellularized.
- 10. Giberson et al teaches a method of microwave-assisted fixation of tissue (see abstract). Giberson teaches that the tissue is suspended in a liquid medium of formalin or aldehyde solutions (see abstract), where the tissue is fully immersed in the medium (see claims 1 and 5), that the tissue, while suspended in formalin solution is irradiated in a microwave oven, while controlling the fluid temperature in the range of 4°C to 40°C, where a cooling effect of the fluid prevents the microwave irradiation from heating the specimen beyond 4°C to 40°C (see claim 6). While these claims are directed to two irradiation times, Giberson teaches that it can be done in a one step microwave oven process (see abstract).
- 11. Giberson teaches that the tissue is placed in a plastic microwave vessel (standard plastic microwave processing cassette), which is placed in a recirculation device placed in the microwave oven and previous filled with a fixative solution. The fixative is pumped from inside the microwave oven through the recirculation device which is external to the microwave oven in order to cool the tissue (see figure 2A and 2B). The entire device set-up is depicted in figures 1A-1D. The circulating fluid would

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result in the loss of some cells prior to complete fixation, thus resulting in decellularization of the suspended tissue.

- 12. Absent evidence to the contrary, and in light of the specification wherein the treating solution comprises fixing reagents, Giberson teaches a method of decellularization tissue comprising immersing said tissue in a liquid medium treating solution, and irradiating the immersed tissue with microwaves from a microwave oven while maintaining the temperature of the tissue in the range between 0 and 40°C by an external cooling apparatus which circulates the cooling liquid. Giberson teaches his method overcomes known problems in the art regarding the use of microwaves on fresh tissue preparations where fixatives are heated in a microwave faster than they are able to penetrate the tissue, thus resulting in the poor fixation of samples (column 2, line 45 through column 3, line 13). Giberson teaches his method is usable on all tissues, including mineralized (ie hard tissue) and non-mineralized tissue (column 4, lines 58-59). Giberson does not teach that the method is performed on mammalian tissue, the types of tissues, or washing the tissues, nor that the treating solution contains a detergent.
- 13. Anderson et al (US Patent No. 5,571,216) teaches a method of tissue welding comprising immersing the tissue in a welding bath (treating solution) and heating the tissue at a temperature of 40°C (column 8, lines 28-37). Anderson specifically teaches mammalian tissue welding on bovine and porcine tissue (column 8, lines 28-43) as well as rabbit tendons and skin (column 9, lines 26-28). Anderson teaches that the welding bath comprises water (column 5, line 30) and that the method further comprises a

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chemical fixation step comprising a solution that contains glutaraldehyde (column 7, lines 18-29). Anderson teaches that welding of cut surface tissues occurs by clamping the tissue together wherein needles are inserted into and through the two tissues, where the needles are supplied with a heated fluid. The hot liquid is collected at the other end of the needles by a similar block with holes for receiving each of the needle tips (column 5, lines 25-40).

14. Anderson's Examples section teaches:

Fresh bovine Achilles tendon and fresh porcine skin were cut into 2 mm thick transverse discs, which were placed between sealed microscope coverslides clamped together and immersed in a circulating water bath at different temperatures for different times. Other samples were welded in a moist atmosphere by heating between two stainless steel temperature controlled plates instrumented with pressure and distance gauges, with equivalent results...After removal from the welding bath, some of the discs were quenched by immersion in a second bath at different temperatures, as low as 0oC, and then assayed for tensile strength (column 8, lines 28-43).

- 15. Thus Anderson teaches that the welding with clamps occurs with the tissue immersed in a circulating water bath, and *then* assayed for tensile strength. He teaches different specific examples of heating in the example, "moist atmosphere" and "water bath" etc, and further teaches that heating can occur via microwaves (see column 3, lines 10-20).
- 16. Anderson teaches that more complicated heating devices can be utilized, including microwave ovens (column 6, lines 1-2). Anderson teaches heating the tissue for a period of 1 hour (column 8, lines 37-39). Anderson teaches that the native tissue to be treated includes vascular vessels as well as parts of whole organs including the gut (column 1, lines 42-45). Finally, Anderson teaches that the method of treatment further comprises a washing step following heating with ice cold physiological saline

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after the weld is complete (column 8, lines 16-24 and 40-41). However, Anderson does not teach that the method is performed wherein the treating solution contains a detergent.

- 17. Essenfeld et al (US Patent 6,207,408) teaches a process for fixing tissues (see abstract). Essenfeld teaches that the fixation technique teaches that the fixing solutions can contain a fixative-dehydrating agent-fat solvent, fixative-dehydrating agent-fat-solvent-clearant, clearant impregnating agent), and microwave energy as a source to achieve uniform heating within the tissue specimens (column 5, lines 8-12). Essenfeld further teaches that the solutions contain detergents:
- 1. the above steps may be accelerated by adding a fixative enhancer, a surfactant, or both to the solutions used in the process. The fixative enhancer may be polyethylene glycol (PEG, mono- and dimethyleneglycol, propylene glycol, polyvinyl pyrrolodone, or the like...The surfactant may also be dimethyl sulfoxide (DMSO), polyxyehtylene sorbitan esters (e.g. TWEEN 80), sodium dimethyl sulfosuccinate, mild house hold detergents, or the like (column 5, lines 17-26).
- 18. Technically, the addition of the fat-solvent, used in the fixation technique using microwaves, removes fat cells from the tissue. This reads on decellularizing the tissue sample that is preserved.
- 19. A skilled artisan would have been motivated to combine the teaching of Giberson on a method of fixing tissues immersed in a fixation solution using a microwave, while maintaining a constant temperature, which Giberson teaches is usable on all tissue types further with the teaching of Anderson on a method of tissue welding and fixation on mammalian tissue which Anderson teaches his welding method is malleable and utilizes different methods specifically to test which heating method produces the strongest weld, and suggests the use of microwave irradiation, further with the teaching

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of Essenfeld on fixating which includes decellularization of the tissue specimens to be preserved that adding detergents to a fixing solution in order to accelerate the fixing process, because the use of Giberson's method would have provided one more heating method already shown to have positive and reliable fixation effects on fresh tissue samples, and Essenfeld's addition of detergents to the solution would further accelerate the fixation technique thereby improving Anderson's method. It would have been obvious to combine the teaching of Giberson on a method of fixing tissue sections with microwaves wherein the tissue is immersed in a coolant comprising a fixative solution with the teaching of Anderson on a method of tissue welding and tissue fixation comprising heating tissue sections using a multiple ways to heat the welding solution further with the teaching of Essenfeld that the addition of detergents to a fixing solution accelerated the fixation method because Giberson and Essenfeld teach their methods result in a faster, more efficient method of fixing tissue and Anderson teaches his method of tissue welding and fixation is malleable and even tests different modes of heating the tissue including the use of microwaves, thus it would have been obvious to improve the method of Anderson and utilize the microwave oven and cooling apparatus of Giberson and detergent solution of Essenfeld in order to further reduce the time and improve the efficiency of Anderson's welding method. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

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20. Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Giberson et al (US Patent 6,875,583) and Anderson et al (US Patent No. 5,571,216) and Essenfeld et al (US Patent 6,207,408) as applied to claim 10 above, and further in view of Kearns et al (US Patent No. 4,963,708). Claim 4 states a method of treating a native tissue of mammalian origin comprising immersing the tissue in a treating solution, and irradiating the immersed tissue with a microwave while maintaining the temperature of the tissue in the range between 0°C ad 40°C wherein the tissue is irradiated with microwaves at a frequency of 2450 MHz for a net period of time from 1 hour to 1 week.

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- 21. Giberson et al (US Patent Publication US20020177183) and Anderson et al (US Patent No. 5,571,216) and Essenfeld et al (US Patent 6,207,408) teach a method of tissue fixation and welding comprising immersing the tissue in a fixation solution comprising a detergent and heating the immersed tissue using a microwave at a temperature of 4 to 40°C by pumping the fixation solution through a cooling apparatus which is outside of the microwave oven for 1 hour (see above). Giberson teaches the microwave is used at 450 W and 250 W, but it can range from 50W to 900 W depending on the tissue (column 5, lines 62-64 and column 6, lines 41-46). Giberson and Anderson teach heating the tissue for a period of 1 hour (column 5, lines 62-64 and column 8, lines 37-39, respectively) however neither Giberson nor Anderson teach using a microwave at 2450 MHz.
- 22. Kearns et al (US Patent No. 4,963,708) teaches a method and apparatus for cooking utilizing a microwave and a double-boiler apparatus. Specifically, Kearns et al

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teaches that, "essentially all domestic microwave ovens operate at 2450 MHz" (Column 1, lines 23-24).

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- 23. The skilled artisan would have been motivated to combine the teachings of Giberson and Anderson and Essenfeld et al on the method of native mammalian tissuefixation and welding comprising the immersion of tissue in a treating solution containing detergent and heating the immersed tissue in a microwave to a temperature of 4-40°C for one hour with the teaching of Kearns that all domestic microwave ovens operate at the frequency of 2450 MHz because doing so would not require a special (ie more expensive or hard to find) microwave oven in order to perform the method. It would have been obvious to the skilled artisan to combine the teaching of Giberson and Anderson and Essenfeld on the method of native mammalian tissue-fixation and welding comprising the immersion of tissue is a treating solution and heating the solution in a microwave to a temperature of 40°C for one hour with the teaching of Kearns that all domestic microwave ovens operate at the frequency of 2450 MHz because using the specific frequency that most microwave ovens already use would allow for easily obtainable and readily available equipment for the artisan utilizing the method of treating native tissue. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.
- 24. Claims 6 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Giberson et al (US Patent 6,875,583) and Anderson et al (US Patent No. 5,571,216)

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and Essenfeld et al (US Patent 6,207,408) as applied to claim 10 above, and further in view of Boyce et al (US Patent No. 6,123,731) of record 7/28/06. Claim 6 states a method of treating a native tissue of mammalian origin comprising immersing the tissue in a treating solution, and irradiating the immersed tissue with a microwave while maintaining the temperature of the tissue in the range between 0°C ad 40°C wherein the native tissue to be treated is hard tissue including bone, cartilage, and teeth (claim 6) and wherein the native tissue to be treated has been pretreated to facilitate the removal of donor cells (claim 9).

- 25. Giberson et al (US Patent Publication US20020177183) and Anderson et al (US Patent No. 5,571,216) and Essenfeld et al (US Patent 6,207,408) teach a method of tissue fixation and welding comprising immersing the tissue in a fixation solution and heating the immersed tissue using a microwave at a temperature of 4 to 40°C by pumping the fixation solution through a cooling apparatus which is outside of the microwave oven for 1 hour (see above). Anderson specifically teaches mammalian tissue welding on bovine and porcine tissue (column 8, lines 28-43) as well as rabbit tendons and skin (column 9, lines 26-28). Giberson teaches his method is usable on all tissues, including mineralized (ie hard tissue) and non-mineralized tissue (column 4, lines 58-59). Neither Giberson nor Anderson teach the native tissue to be treated includes bone, cartilage, or teeth nor that the native tissue is to be pretreated to facilitate the removal of donor cells.
- 26. Boyce et al (US Patent No. 6,123,731) teaches a method of tissue welding comprising immersing human bone fragments (see examples 4 and 5) as well as bovine

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and porcine bones (column 4, lines 1-5) into a treating solution, and heating the tissue using a microwave (column 6, lines 33-43 and column 7 lines 34-36 and claim 28). Boyce also teaches that the bone fragments are demineralized prior to heat treatment by bathing the bone in a 0.6 HCL bath (See examples 1-5).

27. The skilled artisan would have been motivated to combine the teachings of Giberson and Anderson Essenfeld on the method of native mammalian tissue-fixation and welding comprising the immersion of tissue is a treating solution containing detergents and heating the solution in a microwave to a temperature of 40°C for one hour with the teaching of Boyce et al on the method of tissue welding comprising bone and the pretreatment of the bone to remove all donor cells because Giberson teaches his method is appropriate for all tissues including mineralized (hard tissue) tissue and Boyce's teaching broadens the type of hard tissue that the method is capable of treating thereby increasing the applicability for treating multiple tissue types allowing for the treatment of more patients with more transplants and implants all utilizing the same treatment method. Furthermore, the pretreatment of the tissue to remove donor cells would reduce the likelihood for the generation of an immune response in the patient, but also exposes the collagen fibers allowing for crosslinking between bone sheets (Boyce claims 1-4). It would have been obvious to the skilled artisan to combine the teaching of Giberson and Anderson and Essenfeld on the method of native mammalian tissuefixation and welding comprising the immersion of tissue in a treating solution and heating the solution in a microwave to a temperature of 40°C for one hour with the teaching of Boyce on the method of tissue welding comprising bone because the scope

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of the treatment becomes broader, allowing for the treatment of additional diseases and patients with the same methodology. Additionally, the pretreatment of the tissue to remove donor cells would reduce the likelihood for the generation of an immune response in the patient, but also exposes the collagen fibers allowing for crosslinking between bone sheets (claims 1-4). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Response to Arguments

- 28. Applicant's arguments filed on 09/04/07 have been fully considered but they are not persuasive. Applicants traverse the 103(a) rejection over Gibson in view with Anderson. Applicants argue that the art is non-analogous art drawn to fixation rather than decellularization. Thus applicant's contend that both Gibson and Anderson are directed towards preserving tissue and therefore do not read on a method of decellularization, particularly where the claim read requires that the tissue is decellularized. Applicants argue that "decellularization" is an art recognized term which includes "rupturing of cells, and removing cellular membranes, nucleic acids, lipids, and/or pseudoplastinic components" (see page 6 of applicant's response).
- 29. The Examiner is not persuaded by applicant's arguments. The Examiner contends that the methodologies taught by both Gibson and Anderson read on methods

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of decellularization, and that some degree of decellularization occurs during the application of their processes (ie that there is some degrees of cell loss, even if only a single cell). The definition that applicant's provide as an art recognized definition, is in itself broad and encompassing many potential components (referring to "and/or" language used in the definition) thus it appears any one, or more than one can still read on 'decellularization", although none of those components are supported or recited in the instant claim. Thus, using the broadest reasonable interpretation, the loss of a single cell through the process of fixation would read on the instant claims, and any methodology that taught those same steps in the method claims, would also be capable of decellularizing the tissue.

30. Applicants also argue that there was an apparent misconception on the part of the examiner regarding the presence of a fixing solution in the claims examined in the previous office action. Cancelled claim 2 limited the treating solution used in the method of decellularization to a "liquid" solution in the previous claim sets, such an interpretation of a fixing solution was appropriate. Additionally, the open claim language of claim 10, allows for additional components and steps to the claimed methodology. Thus the 103(a) rejection is modified to address the newly limited methodology comprising a solution containing a detergent, and maintained.

Conclusion

- 31. No claims are allowed.
- 32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kam/11/07/07

DAVID GUZO
PRIMARY EXAMINER